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ORIGINS OF THE PROTON NMR CHEMICAL SHIFT NON-EQUIVALENCE IN THE DIASTEREOTOPIC METHYLENE PROTONS OF CAMPHANAMIDES

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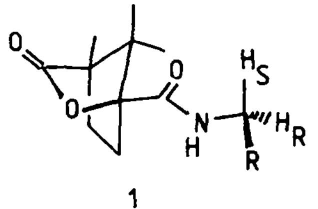
Abstract - The observed chemical shift non-equivalence of the diastereotopic methylene protons in primary camphanamides is rationalized in terms of chirality independent, differential shielding of H_S by the amide carbonyl, as deduced by nmr solution, X-ray structural studies and molecular mechanics calculations.

In proton nmr spectroscopy, the methylene protons at a prochiral centre in a chiral molecule exist in magnetically non-equivalent environments and may exhibit different chemical shifts. It was proposed that the observed chemical shift non-equivalence, $\Delta\delta_{obs.}$, is made up of an intrinsic diastereotopic shielding term, $\Delta\delta_i$ and a conformational term, $\Delta\delta_c$, dependent upon the relative fractional population and the corresponding individual chemical shifts of low-energy molecular conformations.[1] More recently it has been shown that the intrinsic diastereotopic shielding is insignificant in ^1H nmr.[2] The magnitude of the observed chemical shift non-equivalence has been observed to be a function of the separation of the prochiral and chiral centres, of molecular rigidity and of temperature and solvent i.e. parameters which affect the molecular conformation term, $\Delta\delta_c$.[3]

In the ^1H n.m.r. spectra of a series of alkyl camphanamides, 1a-1f, we have found that the pro *S* hydrogen consistently resonates to higher frequency of H_R.[4] This permits the determination of both the enantiomeric purity and the absolute configuration of α-deuteriated primary amines. The chemical shifts of the diastereotopic methylene protons in 1a-f are recorded in Table 1; the pro *R* and pro *S* proton resonances are cleanly separated at medium field in d^6-benzene solvent, with the chemical shift difference between H_S and H_R varying between 0.12 and 0.21 ppm. An example is shown in Figure 1, in which part of the 400 MHz ^1H n.m.r. spectrum of 1d is illustrated. H_S and H_R are clearly separated. Each proton is coupled to the amide NH and to the adjacent methylene protons to give the observed multiplet.



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a) R = Me
b) R = Et
c) R = CH_2CH_2Br
d) R = CH_2Et
e) R = Ph
f) R = *p*-BrPh

In order to probe the origins of the anisochronism of the geminal methylene protons in 1a-f, the para-bromobenzyl derivative 1f has been examined in detail. Examination of molecular models suggests that the observed non-equivalence of the diastereotopic methylene protons is due to the neighbouring amide carbonyl anisotropy.

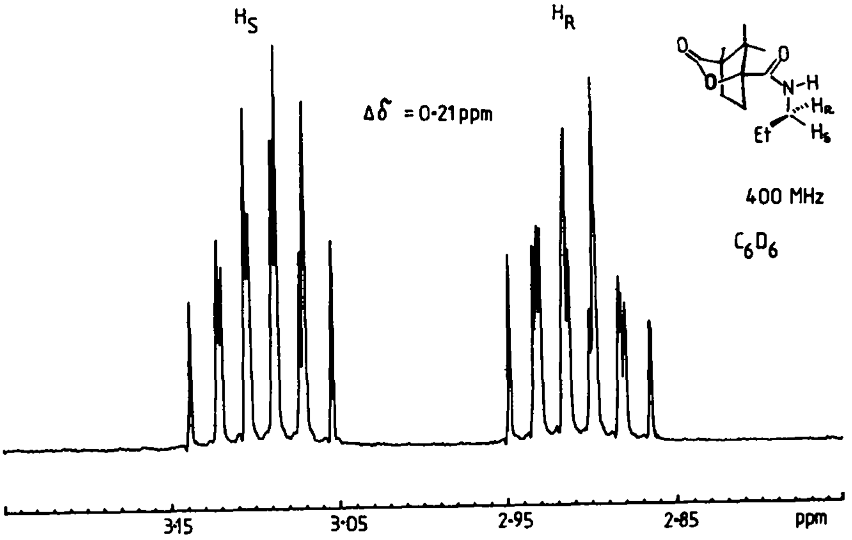

Fig. 1. 400 MHz ^1H n.m.r. spectrum of (1S,4R)-(-)N-propylcamphanamide (1b), showing the diastereotopic methylene protons.

Table 1. NMR Data for Diastereotopic Methylene Protons in 1a-1f[a]

Compound	R	δ_{H_S}	δ_{H_R}	$\Delta\delta_{H_SH_R}$	$J_{H_SH_R}$
1a	Me	3.03	2.89	0.14	17.5
1b	Et	3.12	2.91	0.21	14.3
1c	CH_2CH_2Br	3.00	2.88	0.12	13.7
1d	n-Pr	3.11	2.95	0.16	13.6
1e	Ph	4.25	4.12	0.13	14.8
1f	-p-Br-Ph	4.12	3.96	0.16	14.7

[a] Spectra were recorded in d^6-benzene at 298 K; chemical shifts are given in ppm and coupling constants in Hz.

X-Ray Structural Studies

The structure of 1f has been determined by single crystal X-ray diffraction.[†] There are two independent molecules A and B in the asymmetric unit: these molecules are linked into A-B pairs by NH---O hydrogen bonds between the NH group of one molecule and the lactone carbonyl of another. A view of the two molecules is shown in Figure 2 with the crystallographic numbering scheme. Molecules A and B are conformers related by rotation about the N-C(11) bond with

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[†] Crystals of 1a were grown from $CHCl_3/CCl_4$:hexane (1:1). Crystal data:- $C_{17}H_{20}BrNO_3$, Mr = 366.3, monoclinic, space-group C_2, a = 25.454(6), b = 6.507(3), c = 21.947(7)Å, β = 112.4°, U = 3362(2)Å, Z = 8, D_c = 1.45 g cm^{-3}, F(000) = 1504, $\mu(Mo\text{-}K_\alpha)$ = 24.3 cm^{-1}. At convergence R = 0.064 and Rw = 0.086 for the 1903 observed reflections. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratories, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

simultaneous reorientation of the phenyl ring. The values of the C(10)-N-C(11)-C(12) torsion angles are 96.6 and 286.4° for the A and B molecules respectively. The bromophenyl rings are oriented about the C(11)-C(12) bonds such that the N-C(11)-C(12)-C(13) torsion angles are 31.1 and 325.7° for A and B respectively.

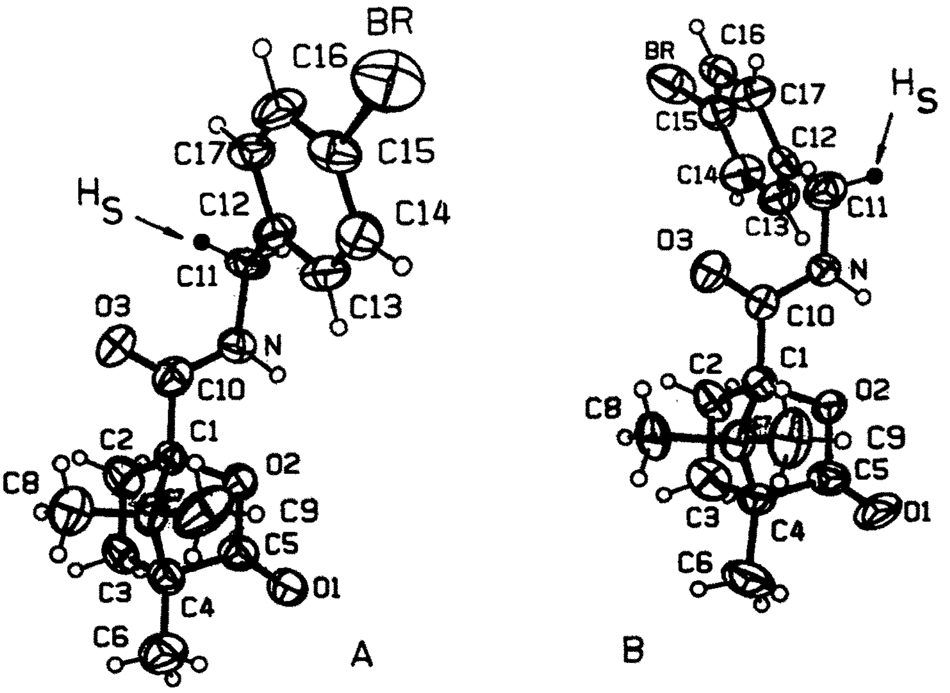

Fig. 2. Molecular structures of the two independent molecules, A (left) and B (right). The relative orientation of the bicyclic ring is the same in both cases.

In molecule A, the pro S hydrogen is closer than H_R to the magnetically anisotropic carbonyl group; in molecule B the situation is reversed. Furthermore, H_S is closer to the amide carbonyl in A than H_R is in B.

Solution N.m.r. Studies

In the ^{1}H n.m.r. spectrum of 1f in d^6-benzene at 298 K, two doublet of doublets may be observed, centred at δ4.11 and 3.95 ppm, corresponding to H_S and H_R respectively. The chemical shift difference between H_S and H_R increases linearly with decreasing temperature, (Table 2); similar behaviour is observed with 1a where $\Delta\delta_{H_SH_R}$ is 0.12 ppm at 320 K and rises linearly to 0.15 ppm at 283 K. The chemical shift difference is independent of amide concentration, precluding any effects due to intermolecular association. Careful examination of the temperature dependence of $\Delta\delta_{H_SH_R}$ reveals that as the temperature is lowered, it is H_S that shifts to higher frequency relative to H_R and other resonances in the molecule. Such behaviour is consistent with H_S spending more time, on average, in a magnetically deshielding environment i.e. proximate to the amide carbonyl.

The observed anisochronism is also sensitive to the n.m.r. solvent used. With 1f, $\Delta\delta_{H_SH_R}$ is a maximum with non-polar aromatic solvents and is lower in polar, aliphatic solvents, (Table 2). Similar behaviour was observed with 1d, with which $\Delta\delta_{H_SH_R}$ at 308 K is 0.03 ppm in $CDCl_3$, 0.05 ppm in CCl_4, 0.06 ppm in d^6-acetone and 0.15 ppm in C_6D_6. The observation that $\Delta\delta_{obs.}$ is a maximum in aromatic solvents suggests that one of the aromatic solvent molecules lies close to the amide group. Some form of weak π-π^* interaction between the aromatic π cloud and the carbonyl double bond may be

Table 2. Variation of $\Delta\delta_{obs.}$ with Temperature and Solvent[a]

Temperature K;	$\Delta\delta_{H_SH_R}$ ppm	Solvent[b];	$\Delta\delta_{H_SH_R}$ ppm
320	0.137	C_6D_6	0.15
310	0.148	C_7D_8	0.14
300	0.162	C_5D_5N	0.09
295	0.171	$CDCl_3$	0.08
290	0.177	$(CD_3)_2CO$	0.07
285	0.185	CD_3OD	0.06

[a] Recorded at 200 MHz.

[b] At 308 K.

involved, enhancing the anisotropic environment experienced by H_S and H_R.

The possibility that the amide N-H may form an intramolecular hydrogen bond with the lactone ether oxygen in non-polar solvents, at the concentrations used in the n.m.r. experiments, was considered. However an FT i.r. study in CCl_4 and C_6D_6 revealed that at concentrations of <u>1f</u> of 10^{-2} M and below, only a single sharp band at 3435 cm^{-1} was observed. This corresponds to the free N-H stretch, and no other bands were observed, in this region, over the concentration range 10^{-5} to 10^{-2} M. At higher concentrations a broad band appeared at 3380 cm^{-1}, which grew as a function of increasing concentration and is assigned to an intermolecular hydrogen bonded NH stretch. In the crystal structure determination, hydrogen bonding between the amide NH of one molecule and the lactone carbonyl of another was revealed. Such interactions also appear to occur in solution at higher concentrations.

Molecular Mechanics Calculations

Using a model of the camphanamide constructed from fragments taken from the Cambridge Crystallographic Database,[5] molecular mechanics conformation energy calculations were performed on <u>1f</u>. The variation in molecular potential energy with changes in torsion angle was calculated by the summation of the separate components for non-bonded, torsional and electrostatic energies, (further details are in Experimental). In <u>Figure 3</u> the variation in molecular potential energy with changes in the C(10)-N-C(11)-C(12) and N-C(11)-C(12)-C(13) torsion angles is illustrated. The contour lines are in energy units of kcal mol^{-1}. Comparison with the observed torsion angles for molecules <u>A</u> and <u>B</u>, revealed by the crystal structure, shows good agreement. Molecule <u>A</u> is the lower energy conformer, residing in the bottom left hand corner of the energy plot, with <u>B</u> in the top right hand corner. The calculated energy difference between <u>A</u> and <u>B</u> is 1.3 kJ mol^{-1}. The local energy minima are calculated to be within 4 kJ mol^{-1} of the absolute energies for the observed crystal conformations, that is, within the limit of the largest probable distortion of a small molecule conformer, in the crystalline state, from the minimum energy form.[6] Furthermore, it is well established that any conformation observed in the crystalline state is likely to be important in solution.[6] Conformer <u>A</u> is the lower energy state and in solution as the temperature is lowered, will be preferentially populated over <u>B</u>.

Conclusions

The studies related above confirm that the observed chemical shift non-equivalence of the geminal methylene protons in camphanamides, <u>1</u>, is due to differential shielding of the diastereotopic methylene protons by the anisotropic amide carbonyl group. In the preferred conformer <u>A</u>, the pro <u>S</u> hydrogen is closer on average to the amide carbonyl group and hence resonates to higher frequency of H_R. As the temperature is lowered this differential shielding is more pronounced as conformer <u>A</u> is preferentially populated. Given that H_S consistently resonates to higher frequency of H_R in all studied camphanamides,[4,7] the rationale put forward may afford a general explanation for the origins of the observed geminal proton anisochronism in camphanamides and related compounds.

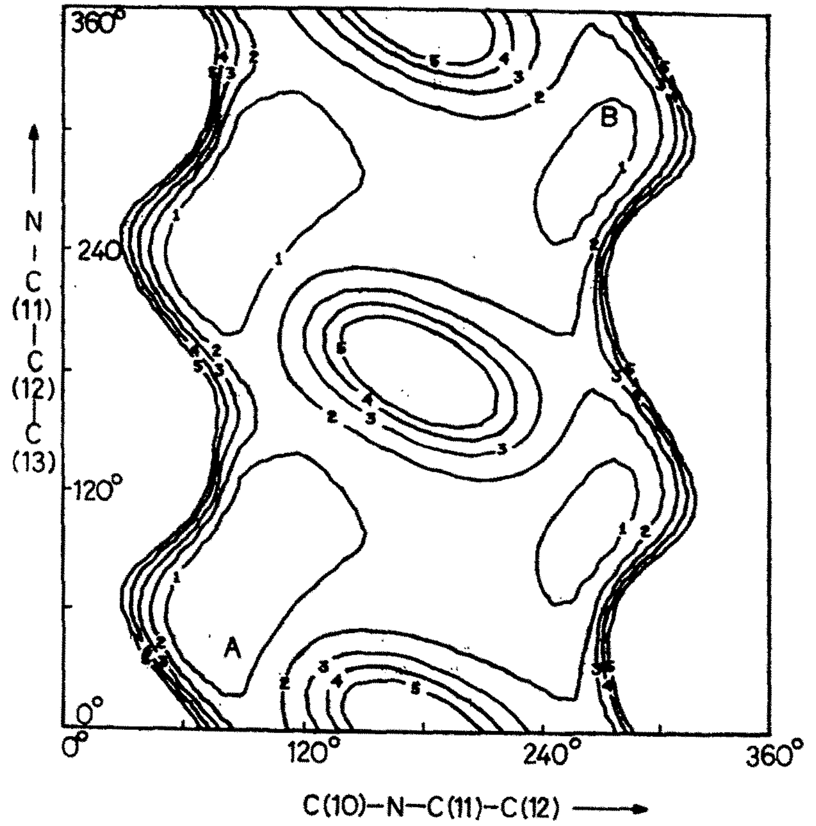

Fig. 3. Molecular potential energy map as a function of the C(10)-N-C(11)-C(12) and N-C(11)-C(12)-C(13) torsion angles. Contours are in 1 kcal mol^{-1} steps.

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded on either a Bruker WH360, a Bruker WP200 or a Bruker WH400 instrument. Molecular mechanics conformational energy calculations were performed on the Glaxo Research molecular modelling system, running on a VAX 11-750 minicomputer coupled to Megatek and Sigma display terminals. The force-field calculations used standard Buckingham and single-term cosine potential functions[8] for the non-bonded and torsional energies, respectively, and the electrostatic energy was calculated from a Coulombic potential using a distance-dependent dielectric term.[9] The associated non-bonded and torsional force-field parameters were set[10] to reproduce in 'rigid-rotor' models (i.e. without full relaxation of molecular geometry), experimental torsional barriers in small molecules[11] and the observed distribution of ϕ, ψ-angles in peptides and proteins.[12] A standard set of partial charges were placed on those atoms involved in potential hydrogen-bonding groups. The crystal structure was determined by the heavy atom method and refined by full matrix least-squares calculations. All hydrogen atoms were located from the difference maps and included but not refined in the calculations. Allowance was made for the anomalous dispersion of bromine. Reflections were measured with a CAD4 diffractometer and all calculations were made with the SDP system of programs on a PDP-11/73 computer system.

The chiral amides 1a-1e were prepared according to literature procedures,[4] and 1f was prepared as described below.

(1S,4R)-(-)-para-Bromobenzylcamphanamide, (1f)

para-Bromobenzylamine hydrochloride (227 mg, 1 mmol) was suspended in dichloromethane (7 cm^3) at 0°C, and triethylamine (150 mg, 1.5 mmol) and (-)-camphanoyl chloride (241 mg, 1.1 mmol) added in sequence. The mixture was stirred for 3 h at 0°C, then poured in sodium hydroxide solution (0.1 M, 50 cm^3) and the aqueous phase extracted with dichloromethane (3 x 10 cm^3). The organic phase was washed with dilute hydrochloric acid (0.1 M, 2 x 20 cm^3), water (2 x 25 cm^3), dried over anhydrous magnesium sulphate, filtered, and solvent removed under reduced pressure to give a colourless solid (220 mg, 60%) which may be recrystallised from chloroform-carbon tetrachloride (1:1) and hexane, mp 126-127°C. Found: C 55.6, H 5.28, N 3.61. $C_{17}H_{20}BrNO_3$ requires C 55.7, H 5.46, N 3.82. δ_H (C_6D_6) 6.77 (1H, br, NHCO), 4.12 (1H, dd, H_S), 3.96 (1H, dd, H_R, $J_{H_SH_R}$ 14.7), 2.30 (1H, m), 1.56 (1H, m), 1.33 (1H, m), 1.25 (1H, m), 0.83, 0.82 (3H + 3H, s + s, Me_2C), 0.69 (3H, s, CMe). m/z 367/365 (M^+), 186/184, 149, 136, 109, 83. ν(KBr) 3380 (H-bonded NH), 2960, 2920, 2860 (m), 1780 (vs, lactone CO), 1675 (vs, NHCO), 1530, 1175.

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